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Short Communication

Prevalence and severity of anemia in pediatric hemodialysis patients, a single center study

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Abstract

BACKGROUNDS: This study was conducted to determine the prevalence and severity of anemia in children and adolescents on chronic hemodialysis, and to identify independent predictors of anemia in children on hemodialysis.

METHODS: This cross-sectional study was performed between September 2005 and January 2006. The study population consisted of 25 patients aged 7−20 years on chronic hemodialysis from pediatric hemodialysis centers in Isfahan.

RESULTS: A total of 22 (88%) patients had hemoglobin levels of <11 g/dL (anemic) and 12 patients (48%) had hemoglobin levels of <8 g/dL (severe anemia). The mean age of these patients was 15.5 ± 3.7 years. Mean time on chronic dialysis was 20.44 ± 15.25 months. Anemia was more common and more severe among children who were on dialysis for less than 6 months. There was an inverse relationship between the severity of anemia and duration of hemodialysis (P = 0.019, r = – 0.465). Nearly all patients were treated with erythropoietin, Children with more severe anemia received slightly higher dose of erythropoietin (P = 0.09, r = 0.202). There was a significant difference between serum albumin values in anemic patients and patients without anemia (P = 0.023). There was a correlation between serum albumin and hemoglobin level (r = 0.511, P = 0.01). Intact PTH levels were >200 pg/ml in 16 patients (66%) and >400 pg/ml in 9 patients (37. 5%). There was a reverse correlation between intact PTH level >200 pg/ml and hemoglobin level (r = -0.505, P = 0.046).

CONCLUSIONS: The prevalence of anemia in hemodialysis children in Isfahan appears to be higher than that reported in the other studies in spite of extensive use of rHuEPO and iron supplementation. We found this to be especially true for patients new on hemodialysis (less than 6 months) and in those with low albumin and severe hyperparathyroidism.

KEY WORDS: Hemodialysis, anemia, children.

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Anemia is a major complication of end-stage renal disease (ESRD) in children [1]. When severe, anemia is associated with cardiovascular dysfunction, cardiomyopathy, and death [2,3]. The major cause of anemia in patients with chronic kidney disease and end-stage renal disease (ESRD) is erythropoietin (EPO) deficiency resulting from decreased production in the kidneys [2,4]. Factors that have been shown to influence the response to rHuEPO in adult and pediatric dialysis patients include dosage, route of administration of erythropoietin, iron, vitamin B_{12} and folate deficiency, acute or chronic infection and aluminum intoxication [1,5]. Refractory anemia appears to be more common in those dialysis patients who also suffer from protein-energy malnutrition (PEM) or inflammation [6] and secondary hyperparathyroidism.

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The objectives of this study were first, to determine the relative frequency and severity of anemia in children and adolescents on chronic hemodialysis, and second, to identify the causative factors for anemia in children on hemodialysis.

Methods

This study was performed between September 2005 and January 2006. The study population consisted of 25 patients on chronic hemodialysis from pediatric hemodialysis centers in Isfahan. All demographic and patient-specific parameters including age, gender, pre- and post-dialysis body weight, height, BMI, cause of ESRD, duration of dialysis (<6 months vs. 6 months and more), access type, dose and route of administration of iron and rHuEPO were recorded. Blood sampling was performed immediately before dialysis to measure hemoglobin level, hematocrit, reticulocyte count, indirect bilirubin, lactic dehydrogenize, serum urea nitrogen, serum iron, ferritin, transferrin, serum calcium, phosphate, intact PTH, CRP, albumin and alkaline phosphates, and perform direct Coombs test. Another blood sample to measure serum urea nitrogen was taken 30 minute after the dialysis session. Data on patient rHuEPO dose (unit/kg/week), and oral iron (mg/kg) or administration of intravenous iron (mg/kg/week) were obtained from dialysis charts. All routine laboratory measurements were performed by Cobas Mira–S using automated methods. Serum intact PTH and ferritin (ng/mL) were measured by a chemiluminescence immunoassay. Serum CRP was obtained to demonstrate the presence or otherwise of an inflammatory state. Anemia was defined as a hemoglobin value less than 11 g/dl and severe anemia as a hemoglobin value less than 8 g/dl. Iron deficiency was defined as ferritin ≤100 ng/dL or percentage transferrin saturation less than 20% and mean corpuscular volume (MCV)<78 fl. Megaloblastic anemia was defined as MCV>100 fl and LDH>190. Serum intact PTH>200 pg/ml was considered as high turnover bone disease secondary to hyperparathyroidism. Kt/v values were calculated using the Daugirdas 2 formula. Adequate dialysis clearance was defined as Kt/v≥1.2 and UUR≥65%.

The results were analyzed using the Statistical Package for Social Sciences (SPSS 11.5) program and expressed as mean and standard deviation. Statistical analysis of data was performed by Spearman and Pearson tests to show correlation between anemia and other variables.

Results

The study group consisted of patients aged 7-20 years. The mean age of hemodialysis patients was 15.5 ± 3.7 years. Mean duration of hemodialysis was 20.4 ± 15.2 months (1–48 months). The mean values of hemoglobin, PTH, transferrin saturation, and albumin are summarized in table 1.

Table 1. Descriptive characteristics of the study population.

Variable	Mean	Minimum	Maximum
Albumin (g/dl)	**3.6 ± 0.66**	**2.7**	**4.8**
EPO dose (unit/kg/wk)	158.56 ± 83.82	66.44	342.85
PTH (pg/ml)	872.5 ± 878	20	1110
Ferritin (ng/ml)	872.5 ± 878.2	65	4269
MCV (fl)	90.66 ± 10.95	60	118.5
Iron (mcg/ml)	90.60 ± 54.24	25	225
Transferring saturation (%)	33.92 ± 20.07	8.33	75

Twenty-two patients (88%) had hemoglobin values less than 11 g/dL (anemia) and 48% (12 patients) had hemoglobin values less than 8 g/dL (severe anemia). All of the patients who were on dialysis for less than 6 months had anemia (100%). There was an inverse correlation between severity of anemia and duration of hemodialysis (P = 0.019, r = –0.465) (figure 1).

There was no correlation between age and gender and hemoglobin (P = 0.30 and P = 0.29 respectively). Nearly all children (92%) were treated with erythropoietin with no difference between the routes of administration. No correlation was seen between erythropoietin dose and Hb level (P = 0.4). Absolute iron defi-

ciency (defined as TSAT<20% and ferritin<100 ng/mL) was seen in one patient. The mean value of kt/v was 1.62 ± 0.86, and of URR was 0.68 ± 0.13. No correlation was seen between URR, kt/v and Hb level (P = 0.7, P = 0.5 respectively).

Children with anemia were less likely to have normal serum albumin. There was a significant difference between serum albumin level in anemic and non-anemic patients (P = 0.023). The mean albumin level was 4.4 g/dl, 3.63 g/dl, and 3.35 g/dl in patients with Hb>11, 11<Hb<8, and Hb<8, respectively (P = 0.047). There was a correlation between serum albumin and hemoglobin level (r = 0.511, P = 0.01) (figure 2). A reverse correlation was seen between intact PTH level >200 pg/ml and hemoglobin level (r = −0.505, P = 0.046) (figure 3).

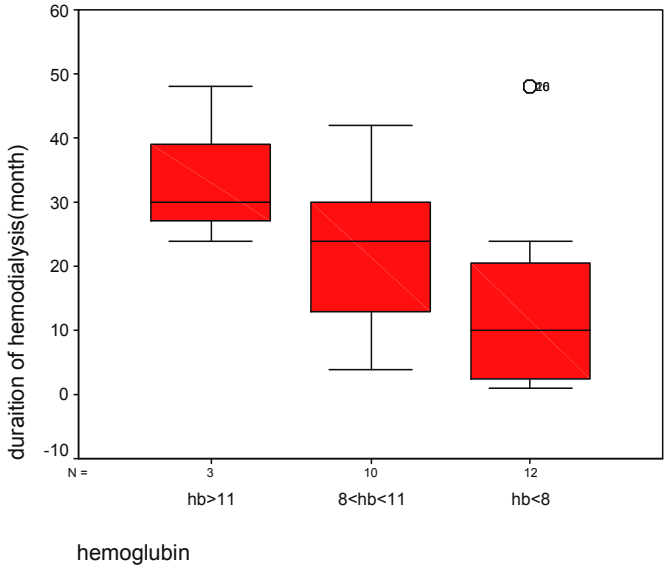

Figure 1. Duration of hemodialysis (months) in patients with target hemoglobin Hb<11 mg/dl, mild to moderate anemia (8<Hb<11) and severe anemia Hb<8 mg/dl.

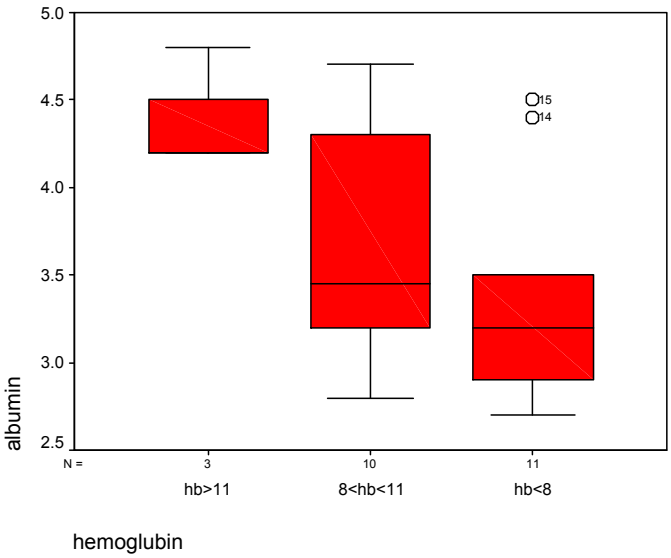

Figure 2. Serum albumin levels (g/dl) in patients with target hemoglobin Hb>11 mg/dl, mild to moderate anemia (8<Hb<11) and severe anemia Hb<8 mg/dl.

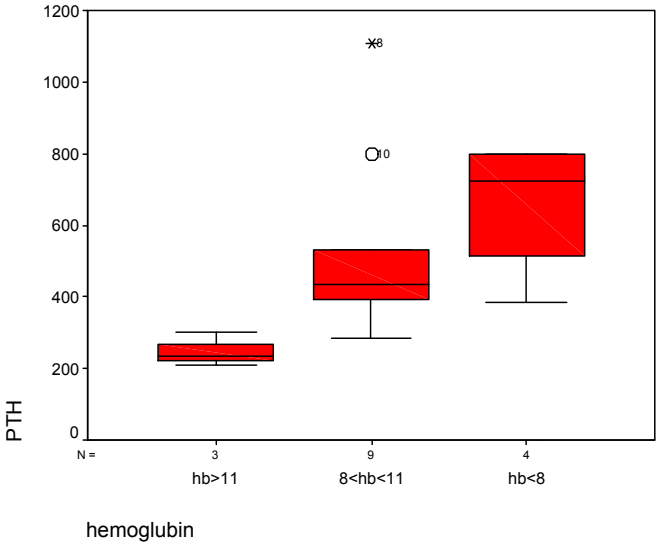

Figure 3. Serum intact PTH levels more than 200 pg/ml in patients with target hemoglobin Hb<11 mg/dl, mild to moderate anemia (8<Hb<11) and severe anemia Hb<8 mg/dl.

Discussion

Despite the extensive use of erythropoietin and iron supplements, 88% of children maintained on chronic hemodialysis had a mean hemoglobin level of less than 11 g/dl.

In initial analysis, lower serum albumin, inflammation and severe hyperparathyroidism were factors that correlate with anemia in these patients with anemia. Previous studies showed that 37-63% of pediatric patient on hemodialysis had anemia despite receiving erythropoietin. The recommended starting dosage of rHuEPO is 50-150 U/kg given three times weekly [2]. Our patients received mean weekly rHuEPO doses of 158 U/kg and these doses were significantly higher than those received by adults.

Fadrowski et al showed that increasing age and dialysis for less than 6 months were predictive of anemia [7]. There was no correlation between age, gender and anemia in our study, but patients new on dialysis (treated for less than 6 months) were more anemic. The nature of causative disease, degree of anemia prior to the onset of dialysis and delay in eprex administration may account for this finding but this could not be statistically assessed from the data pool.

Some patients do not respond to rHuEPO therapy even if high doses are used. A reason for EPO resistance is iron depletion or insufficient access to iron storage pools [8]. Iron supplements had been prescribed for almost all of our patients. There are not any standards for iron adequacy in hemodialysis children. Iron adequacy in adult dialysis patients has been defined as a serum ferritin concentration >100 ng/ml and percentage transferrin saturation of >20% [9]. Serum ferritin >10 ng/ml and percentage transferrin saturation as low as 7% are considered normal for healthy children [10]. Serum ferritin >40 ng/ml has been reported to be adequate in children on dialysis [11]. According to adult dialysis protocol one of our patients had iron deficiency anemia (ferritin<100, TSAT <20%).

Megaloblastic anemia (MCV>100 fl and LDH>190) was seen in 3 patients (12%) and serum albumin was less than 3.5 mg/dl in all. We did not measure serum folate and vitamin B_{12} level in these patients but nearly all cases of megaloblastic anemia in children are due to B_{12} and folate deficiency [12] and megaloblastic anemia may have been a manifestation of poor nutrition in our patients.

Insufficient dialysis is associated with significant clinical morbidity and an increased

risk of mortality, and it likely contributes to anemia [13,14]. Frankenfield et al showed that dialysis clearance no longer appeared to be an important factor accounting for the anemia in pediatric hemodialysis patients [3]. The mean dialysis adequacy (Kt/V 1.62 ± .86) for our children dialyzed exceeded the K/DOQI clearance guidelines for adult hemodialysis patients (Kt/V≥1.2). Although dialysis clearance was inadequate in 5 patients (20%), there was no correlation between dialysis clearance and hemoglobin level in this study.

Severe secondary hyperparathyroidism appears to be important in the severity of anemia in children with chronic renal failure [1]. PTH may be a direct inhibitor of endogenous erythropoietin production [15]. Another mode of action of PTH in ESRD may be an increase in red blood cell osmotic fragility, leading to decreased red blood cell survival time in affected patients [16]. Synthetic PTH or serum from hyperparathyroid patients has been reported to inhibit red blood cell precursors in vitro in some studies [17]. Hyperparathyroidism may also affect anemia by causing bone marrow fibrosis, which reduces the available space for erythroid-forming units [18]. A serum intact PTH level >200 pg/ml has been shown previously to be strongly predictive of osteitis fibrosa in children [19]. PTH effect on erythropoiesis can be overcome by higher doses of rHuEPO [1]. The presence of severe hyperparathyroidism could adversely influence the response to erythropoietin [1]. PTH levels >200 pg/ml were seen in more than half of our patients and more than one-third of them had PTH levels >400 pg/ml. There was a reverse correlation between intact PTH level >200 pg/ml and hemoglobin level in our study.

Low serum albumin and anemia were related in adult patients maintained on hemodialysis but in the context of inadequate dialysis clearance [13]. Frankenfield et al raised the possibility that two variables, anemia and albumin, are associated independent of dialysis clearance in pediatric patients and support the view that poor nutrition may be an additional factor for anemia [3]. Improving nutritional state in dialysis patients may improve anemia and lead to lower EPO requirement. In a meta-analysis by Hurot et al [20], L-carnitine administrations, used to improve nutritional state, were associated with improved hemoglobin level and decreased EPO dose and EPO resistance in anemic dialysis patients. Nearly half of our patients were hypoalbuminemic (albumin <3.5 g/dl). There was also a correlation between serum albumin and hemoglobin level in this study.

Refractory anemia appears to be more common in dialysis patients who also have PEM and/or inflammation [21,22]. Several previous studies reported an association between anemia and inflammation in dialysis patients, reflected by a high serum concentration of CRP [22]. Serum levels of ferritin, a marker of iron stores and also a positive acute-phase reactant, have been shown to be paradoxically high in patients with ESRD with refractory anemia [23,24]. Increased ferritin production may prevent iron delivery to erythrocyte precursors [23]. Moreover, uptake of iron is lower than usual in inflammation [25]. IL-1 and TNF-α, have been shown to inhibit EPO production in vitro [26]. Furthermore, increased release or activation of such inflammatory cytokines as IL-6 or TNF-α has been shown to have a suppressive effect on erythropoiesis [27]. Finally, Patients with inflammation may be more prone to gastrointestinal bleeding [25]. Evidence of inflammation existed in 5 patients in this study with serum ferritin>1000 ng/ml and positive CRP.

Conclusions

Pediatric chronic hemodialysis patients in Isfahan may be undertreated for anemia despite the extensive use of rHuEPO supplementation. Iron deficiency was not a major cause of anemia in our study. Severe hyperparathyroidism, malnutrition, and inflammation should be considered as major causes of anemia in this study, the results of which indicate the need for improvement in the management of anemia in children undergoing chronic hemodialysis.

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